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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,162	03/16/2001	Manuela Martins-Green	407E-000500US	5788

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	22

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,162	MARTINS-GREEN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 87-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8 and 87-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 July 2003 (Paper No. 19) has been entered.

Status of Application, Amendments and/or Claims

The amendment filed 21 July 2003 (Paper No. 20) has been entered in full. Claims 1, 3, 4, 19 were cancelled. New claims 94-101 were added. Claims are 6-8, 87-101 are under examination.

The information disclosure statement filed 21 July 2003 (Paper No. 21) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8, 89, 91, 96 and 99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "no greater than about 15 amino acids in length" and "no greater than about 8 amino acids in length". Applicant's amendment, filed 21 July 2003 (Paper No. 20), asserts that no new matter has been added and directs support to page 26, lines 26-31, for the written description for the above-mentioned "limitations". However, the specification states, chemokine fragments useful in the invention can, for example, range from about 5 to about 50 amino acids in length, although other lengths are possible. Preferred fragments range from about 8 to about 25 amino acids, and preferably from about 8 to about 15 amino acids. So the upper limit contemplated was greater "than about 8" and "than about 15". The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, applicant is invited to provide additional written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claims 6, 7, 87, 89, 91-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims (6 and 7) are drawn to a composition comprising a polypeptide comprising a single interleukin-8 (IL-8) fragment and a pharmaceutically acceptable carrier, wherein said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif and an amino acid sequence that is at least 70% (or 90%) identical to an N-terminal amino acid sequence of IL-8, and is not greater than about 15 amino acids in length, wherein the N-terminal amino acid sequence comprises a subsequence of residues 1-36 of SEQ ID NO:5 or residues 1-38 of SEQ ID NO:4. Thus the claims are drawn to an amino acid sequence that is at least 70% (or 90%) identical to *any* 15 amino acid fragment within residues 1-36 of SEQ ID NO:5 or residues 1-38 of SEQ ID NO:4 which comprises an ELR motif.

The instant claims (89 and 91) are also drawn to a polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, comprises an ELR motif and is not greater than about 15 amino acids in length, and wherein the IL-8 fragment comprises an amino acid sequence variant of SEQ ID NO:8 (SAKELR) [or SEQ ID NO:9 (AVLPRSAKELR)], wherein the amino acid sequence variant has a conservative amino

acid substitution of one amino acid of SEQ ID NO:8 (SAKELR) [or SEQ ID NO:9 (AVLPRSAKELR)].

The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites (see Wells, 1990, Biochemistry 29:8509-8517). These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. For instance, Herbert *et al.* (The Journal of Biological Chemistry, Vol. 266/28 pages 18989-18994, 1991) teach the conservative substitution of one amino acid in a sequence comprising SEQ ID NO:8 and SEQ ID NO:9 of interleukin-8 (IL-8). The conservative substitution of Leu for Ala at residue 5 lead to inactivation of IL-8. In addition, the replacement of Glu at position 4 or Arg at position 6 with Ala lead to inactivation of IL-8 (page 18990, Figure 1 and Table 1).

Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the *specific positions* in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), the nature and extent of changes that can be made in these positions while still maintaining the function of stimulating the differentiation of fibroblasts to myofibroblasts.

Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate and screen IL-8 variants for the activity of stimulating the differentiation of fibroblasts to myofibroblasts, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of protein folding on structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-8, 88, 90, 92, 95, 97, 98, 100 and 101 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern *et al.*, US Patent No. 5,641,867.

Claims 6 and 7 are drawn to a composition comprising a polypeptide comprising a single interleukin-8 (IL-8) fragment and a pharmaceutically acceptable carrier, wherein

said IL-8 fragment stimulates the differentiation of fibroblasts to myofibroblasts, and wherein said fragment comprises an ELR motif and an amino acid sequence that is at least 70% (or 90%) identical to an N-terminal amino acid sequence of IL-8, and is not greater than about 15 amino acids in length, wherein the N-terminal amino acid sequence comprises a subsequence of residues 1-36 of SEQ ID NO:5 or residues 1-38 of SEQ ID NO:4.

Claim 8 is drawn to a composition comprising a polypeptide comprising a single interleukin (IL-8) fragment and a pharmaceutically acceptable carrier, wherein, the IL-8 fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NO:8 and SEQ ID NO:9, and is no greater than about 15 amino acids in length.

Claims 88 and 90 are drawn to a polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein said IL-8 fragment consist of amino acid sequence SAKELR (SEQ ID NO:8) or AVLPRSAKELR (SEQ ID NO:9).

Stern teaches a peptide derived from the ELR-region of IL-8 (SEQ ID NO:17). The peptide of Stern comprises the ELR motif and is 12 amino acids long. Stern teaches an IL-8 fragment which comprises the amino acid sequence of SEQ ID NO:8 and is 100% identical. Stern teaches an IL-8 fragment which comprises the amino acid sequence of SEQ ID NO:9 and is 100% identical. The peptide of Stern (SEQ ID NO:17) is one amino acid longer than SEQ ID NO:9 (column 21, lines 55-57 and column 41-42 and sequence query, Appendix A and B). Thus, the peptide of Stern is a polypeptide comprising a single interleukin-8 (IL-8) fragment, wherein the IL-8 fragment consist of amino acid sequence SAKELR (SEQ ID NO:8) or AVLPRSAKELR (SEQ ID NO:9). The

IL-8 fragment of Stern comprises a subsequence of residues 1-36 of SEQ ID NO:5 or residues 1-38 of SEQ ID NO:4. The IL-8 fragment of Stern is expected to have the property of stimulating the differentiation of fibroblasts to myofibroblasts because a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)) Water can be considered a pharmaceutically acceptable carrier.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
October 16, 2003

YVONNE EYLER, PH.D
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